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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,637	02/06/2007	Dieter Scheller	6102-000034/US/NP	2828

28997 7590 10/16/2008
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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,637	SCHELLER ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-21* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *10-14 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 10-21 are currently pending. Claims 15-18 are withdrawn. Claims 1-9 are cancelled. Accordingly, claims 10-14 and 19-21 are the subject of this Office Action. This is the first Office Action on the merits of the claims.

Information Disclosure Statement

2. None provided.

Priority

3. The earliest effective filing date afforded the instantly claimed invention has been determined to be 12/13/2004 as to claims 10-14 and 19-21.

4. Acknowledgment is made of Applicant's claim for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on a prior application filed in Germany on 12/18/2003. The certified copy has been filed in parent Application No. PCT/EP04/14143, filed on 07/12/2005.

Election/Restrictions

5. Applicant's election with traverse of Group I, drawn to compounds and compositions, in the reply filed on 09/23/2008 is acknowledged. Applicant traverses on the grounds that *van Vliet et al* (J Med Chem 39:4233-4237) does not anticipate the instant invention. However, Applicant's argument is moot since, as acknowledged by Applicant, *Swart et al* (J Analyt Toxicol 18:71-77, 1994) discloses "the (S)-enantiomer of 2-N-propylamino-5-hydroxytetralin" (Applicant's Specification, Page 2, Paragraph 0012). Furthermore, as evidenced by Figure 4, (S)-2-N-propylamino-5-hydroxytetralin was

subjected to LC/MS which entails that the compound was in solution with at least water, which encompasses a "pharmaceutical composition comprising (S)-2-N-propylamino-5-hydroxytetralin… and at least one pharmaceutically acceptable carrier or adjuvant" as recited by instant claim 10. Accordingly, the special technical feature of instant claim 1 is still not novel. The requirement is still deemed proper and is therefore made FINAL.

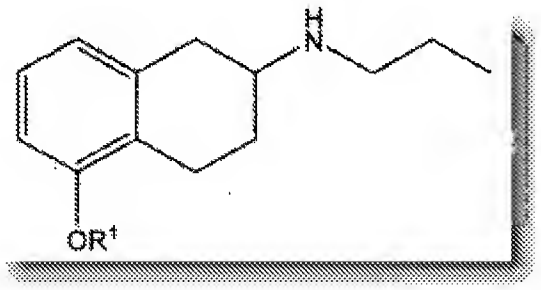
Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **Claims 10-14 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

8. Instant claims 10 and 19 are drawn to compounds having the general formula



(claim 19) and compositions thereof (claim 10). It is unclear and the specification does not provide clarification as to the meaning the of the term "general formula". The term “general” is a broad term. As such, the claims - which are drawn to compounds having the above “general formula” - encompass compounds in addition to compounds having the exact formula above. Yet, there is no guidance as to which additional compounds are encompassed by the claims. Since one

of ordinary skill in the art would not be able to discern which additional compounds are encompassed by the claims, the claims are invalid for indefiniteness.

9. Accordingly, instant claims 10 and 19 are indefinite. Additionally, dependent claims 11-14 and 20-21, which fail to render the term definite, are also rejected as indefinite.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

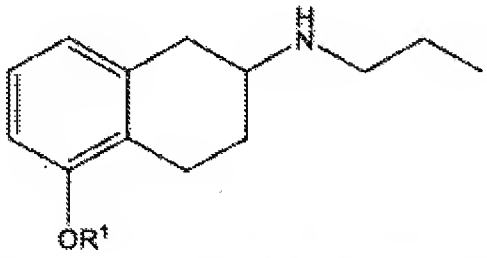
11. **Claims 10-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by *Swart et al* (J Analyt Toxicol 18:71-77, 1994) provided by Applicant.**

12. Instant claims 10-11 are drawn to pharmaceutical compositions "comprising (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier or adjuvant" (claim 1), more specifically wherein the composition comprises "(S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt thereof" (claim 2). As acknowledged by Applicant, *Swart et al* (J Analyt Toxicol 18:71-77, 1994) "disclose the (S)-enantiomer of 2-N-propylamino-5-hydroxytetralin" (Applicant's Specification, Page 2, Paragraph 0012). Specifically, *Swart et al* identified the compound as a metabolite of S(-)-2-*N*-propyl-*N*-2-thienylethylamino-5-hydroxytetralin (N-0923) using HPLC with UV detection, combined with atmospheric pressure ionization mass spectrometry (entire

document and Page 74, Figure 2, Metabolite 4). In being subjected to LC/MS (as evidenced by Page 75, Figure 4), the compound was necessarily in solution comprising at least water. As such, the solution encompasses a "pharmaceutical composition comprising (S)-2-N-propylamino-5-hydroxytetralin… and at least one pharmaceutically acceptable carrier or adjuvant" as recited by claims 10-11. Accordingly, instant claims 10-11 and 14 are anticipated.

13. **Claims 10 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by *Daas et al* (Nauyn-Schmiedeberg's Arch Pharmacol 342:655-659, 1990)**.

14. Instant claim 10 and 12 are drawn to pharmaceutical compositions "comprising (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier or adjuvant, wherein the prodrug is of the **general** formula



wherein R^1 is selected from the group consisting of acyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, acetal, ketal, $-C(O)NR^2R^3$, $-C(O)NHR^2$, $-P(O_2H)OR^2$ and $-P(O_2H)R^2$,

wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, benzyl and phenyl,

" (claim

10, emphasis added). More specifically, claim 12 is drawn to the composition of instant claim 10 wherein the composition comprises a prodrug or salt thereof; and claim 13 is drawn to the composition of instant claim 10 adapted for transdermal, transmucosal or parenteral delivery;

15. *Daas et al* specifically teach the following:

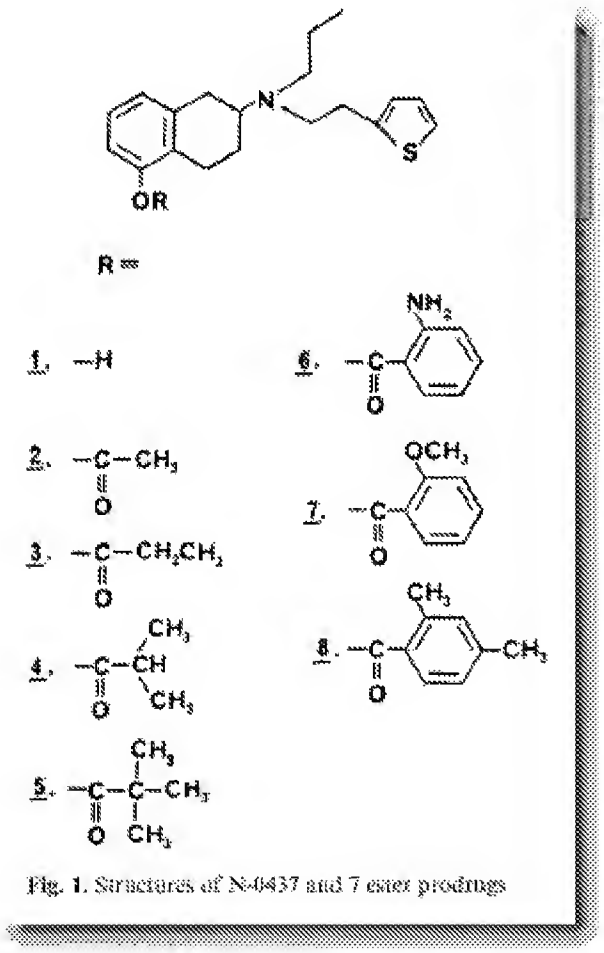


Fig. 1. Structures of N-0437 and 7 ester prodrugs

As discussed above, the term “general” in instant claim 10 is indefinite. However, it is clear from the above disclosure that *Daas et al* teach prodrugs having the **general** formula recited by instant claim 10. Moreover, *Daas et al* teach that “For transdermal application, the HCl salts were converted into the free bases and dissolved in an alcohol and polyethyleneglycol-400 mixture (6:4)" which

encompasses a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier or adjuvant as recited by instant claim 10 and adapted for transdermal delivery as encompassed by instant claim 13. Accordingly, claims 10 and 12-13 are anticipated.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

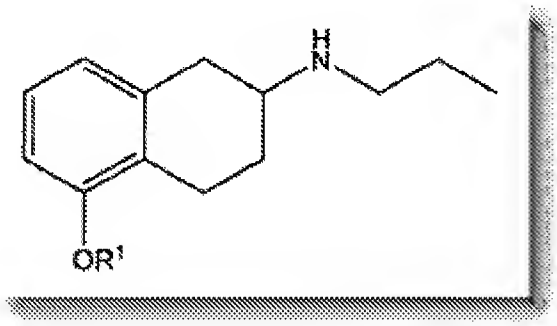
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. **Claims 10-12, 14 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hacksell et al* (J Med Chem 22(12):1469-1475, 1979) in view of *Wikstrom et al* (J Med Chem 28:215-225, 1985) and *Rodenhuis* (New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation, 2000)**.

20. Instant claims 19-21 are drawn to compounds of the general formula



in the (S)-configuration that, when administered to a human body, are cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin.

21. *Hacksell et al* clearly teach that racemic 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist (Page 1472, Table I, compound 8), which is acknowledged by Applicant (Applicant's Specification, Pages 1-2, Paragraphs 0007-0008). Although Applicant states that "aminotetralins with N,N-dialkylation were the most active and appropriate compounds for the intended oral administration" (Applicant's Specification, Page 2, Paragraph 0008) it is still the case that racemic 2-N-propylamino-5-hydroxytetralin demonstrates significant agonistic activity. In fact, racemic 2-N-

propylamino-5-hydroxytetralin is significantly more potent that apomorphine (Pages 1472-1473, Table I, compare compounds 8 and apomorphine). Accordingly, one of ordinary skill in the art would have been motivated to formulate compounds and compositions containing 2-N-propylamino-5-hydroxytetralin. However, *Hacksell et al* do not teach the (S) enantiomer of 2-N-propylamino-5-hydroxytetralin, nor do they teach a prodrug thereof.

22. *Wikstrom et al* teach enantiomeric separation of related aminotetralins to increase dopamine agonistic activity. Specifically, *Wikstrom et al* investigated the potency of enantiomers of the structurally and functionally related compound 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT) which "have been classified as less potent in the previous studies" (Page 217, Column 1, Paragraph 3). Significantly, *Wikstrom et al* report that the (S) enantiomer of the compound, having an ED_{50} of 3.7 nmol/kg, was significantly more potent than the racemic compound (Page 219, Table III, compound 1(S)) having an ED_{50} of 11 nmol/kg (Page 219, Column 2, Paragraph 6). Accordingly, one of ordinary skill in the art at the time the invention was made would have been motivated to subject 2-N-propylamino-5-hydroxytetralin to enantiomeric separation, and would have been especially motivated to select the (S) enantiomer of the compound.

23. *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration. A major disadvantage of the hydroxylated 2-aminotetralins and other phenolic compounds is that they undergo considerable inactivation by glucuronidation in the gut and the liver. One of the strategies to circumvent the problem

of the low oral bioavailability of the hydroxylated 2-aminotetralins is to search for suitable prodrugs. Frequently investigated prodrugs of phenols are esters and carbamates" (Page 98, Chapter 6, Introduction, Paragraph 3). Thus, one of ordinary skill in the art would have been motivated to formulate prodrugs of (S) 2-N-propylamino-5-hydroxytetralin.

24. In summary, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of *Hacksell et al* - which clearly teach that 2-N-propylamino-5-hydroxytetralin is a potent dopamine agonist - with the teachings of *Wikstrom et al* - which clearly teach that the (S) enantiomer of a structurally and functionally related compound is more potent than its racemic form. Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate suitable prodrugs of (S) 2-N-propylamino-5-hydroxytetralin in light of *Rodenhuis*, which provide the motivation to search for prodrugs encompassed by claims 19-20. Thus, claims 19-20 are *prima facie* obvious. Additionally, the obvious compound would necessarily be cleaved, processed or metabolized to 2-N-propylamino-5-hydroxytetralin upon administration to a human body, as recited by claim 21. Accordingly, claim 21 is also *prima facie* obvious.

25. Claims 10-12 and 14 are drawn to compositions containing (S) 2-N-propylamino-5-hydroxytetralin or a prodrug thereof (claims 10-12 and 14). As discussed above, *Hacksell et al* in view of *Wikstrom et al* and *Rodenhuis* teach (S) 2-N-propylamino-5-hydroxytetralin and prodrugs thereof. Moreover, *Hacksell et al* and *Wikstrom et al* specifically teach that "All substances to be tested were dissolved in saline immediately

before use" (Pages 224 and 1474, respectively, Pharmacology Section), which encompasses compositions containing a pharmaceutically acceptable carrier or adjuvant.

26. **Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hacksell et al* (J Med Chem 22(12):1469-1475, 1979) in view of *Wikstrom et al* (J Med Chem 28:215-225, 1985) and *Rodenhuis* (New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation, 2000) as applied to claims 10-12 and 14 above, in further view of *Jansen et al* (Naunyn-Schmiedeberg's Arch Pharmacol 343-134-142, 1991).**

27. As discussed above, claims 10-12, 14 and 19-21 are taught by *Hacksell et al* in view of *Wikstrom et al* and *Rodenhuis*. However, none of the prior art teach the composition adapted for transdermal, transmucosal or parenteral administration as recited by instant claim 13.

28. As discussed above, *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration" and suggests formulating prodrugs to overcome this problem (Page 98, Chapter 6, Introduction, Paragraph 3). Additionally, *Jansen et al* teach "two ways to circumvent this first-pass effect… transdermal application… and oral administration of ester prodrugs" (Page 134, Column 2, Paragraph 1). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to adapt the compositions for transdermal delivery. Thus, claim 13 is *prima facie* obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
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